

# Infertility

## Epidemiology

- 10-15% of couples, must investigate both members of the couple

## Female Factors

### Etiology

- age
- chemotherapy
- ovulatory dysfunction (15-20%)
  - hypothalamic (hypothalamic amenorrhea)
    - ♦ stress, poor nutrition, excessive exercise (even with presence of menstruation), history of eating disorders
  - pituitary (prolactinoma, hypopituitarism)
  - ovarian
    - ♦ PCOS
    - ♦ primary ovarian insufficiency
    - ♦ luteal phase defect (poor follicle production, premature corpus luteum failure, failed uterine lining response to progesterone), poorly understood
  - systemic diseases (thyroid, Cushing's syndrome, renal/hepatic failure), diabetes
  - congenital (Turner's syndrome, gonadal dysgenesis, or gonadotropin deficiency)
- outflow tract abnormality (15-20%)
  - tubal factors (20-30%)
    - ♦ PID
    - ♦ adhesions (previous surgery, peritonitis, endometriosis)
    - ♦ ligation/occlusion (previous ectopic pregnancy)
  - uterine factors (<5%)
    - ♦ congenital anomalies, bicornuate uterus, septate uterus, prenatal DES exposure, intrauterine adhesions (e.g. Asherman's syndrome), submucosal fibroids/polyps
    - ♦ infection (endometritis, pelvic tuberculosis)
  - cervical factors (5%)
    - ♦ hostile or acidic cervical mucus, anti-sperm antibodies
    - ♦ structural defects (cone biopsies, laser or cryotherapy)
- endometriosis (15-30%)
- multiple factors (30%)
- unknown factors (10-15%)

### Investigations

- ovulation
  - day 3: FSH, LH, estradiol, TSH, prolactin, free and total testosterone, androstenedione, DHEAS, free testosterone
  - day 21-23: high serum progesterone levels confirm ovulation
  - general health: CBC, Fe, A1c
- tubal factors
  - hysterosalpingogram (HSG) – dye insufflated into uterus and x-ray taken
    - ♦ shows uterine cavity shape and if tubes are patent
    - ♦ can be therapeutic – opens fallopian tube
  - sonohysterogram (SHG) – saline insufflated into uterus and ultrasound done
    - ♦ shows uterine cavity shape and if tubes are patent
    - ♦ can be therapeutic and open the tubes
  - laparoscopy with dye insufflation (or tubal dye test) rarely done as diagnostic
- peritoneal/uterine factors
  - HSG/SHG, hysteroscopy
- other
  - karyotype
  - anti-mullerian hormone (AMH) – a test of ovarian reserve, the higher the number the better



**Infertility:** inability to conceive or carry to term a pregnancy after 1 yr of regular, unprotected intercourse

**Primary infertility:** infertility in the context of no prior pregnancies

**Secondary infertility:** infertility in the context of a prior conception

Generally, 75% of couples achieve pregnancy within 6 mo, 85% within 1 yr, 90% within 2 yr



#### When Should Investigations Begin?

- <35 yr: after 1 yr of regular unprotected intercourse
- 35-40 yr: after >6 mo of regular unprotected intercourse
- >40 yr: immediately

#### Earlier if:

- History of PID
- History of infertility in previous relationship
- Prior pelvic surgery
- Chemotherapy/radiation in either partner
- Recurrent pregnancy loss
- Moderate-severe endometriosis



#### Ethical Considerations in Infertility Treatment

- Infertility demands non-judgmental discussion
- Ethical issues surrounding surrogacy, donor gametes, and other advanced reproductive technologies are still evolving and remain controversial
- If the physician finds that certain treatment options lie outside of their moral boundaries, the infertile couple should be referred to another physician

## Treatment

- lifestyle modifications (quit smoking/cannabis, reduce caffeine/alcohol intake, healthy diet, exercise, etc.)
  - education: timing intercourse relative to ovulation (have sex every other day from 2 d prior to 3 d following presumed ovulation)
- medical
  - ovulation induction
    - ♦ clomiphene citrate (Clomid®): estrogen antagonist used in anovulatory patients
      - blocks brain's perception of circulating estrogen, resulting in increased release of FSH and LH which can help to induce ovulation (better results if anovulatory)
      - followed by  $\beta$ -hCG for stimulation of ovum release
    - ♦ letrozole: aromatase inhibitor; may be associated with a higher rate of live births in patients with PCOS
  - may add:
    - ♦ bromocriptine (dopamine agonist) or carbamazepine if elevated prolactin
    - ♦ metformin (for PCOS)
    - ♦ luteal phase progesterone supplementation for luteal phase defect (mechanism not completely understood)
    - ♦ anticoagulation and ASA (81 mg PO once daily) for women with a history of recurrent spontaneous abortions (for antiphospholipid antibody syndrome)
    - ♦ thyroid replacement to keep TSH <2.5
- surgical/procedural
  - tubuloplasty
  - lysis of adhesions
  - artificial insemination: intracervical insemination (ICI), intrauterine insemination (IUI), intrauterine tuboperitoneal insemination (IUTPI), intratubal insemination (ITI)
  - sperm washing
  - IVF
  - intrafallopian transfer (IFT)
  - GIFT\*: immediate transfer with sperm after oocyte retrieval
  - ZIFT\*: transfer after 24 h culture of oocyte and sperm
  - TET\*: transfer after >24 h culture
  - ICSI
  - IVM
  - $\pm$  oocyte or sperm donors
  - $\pm$  pre-genetic screening for single gene defects in karyotype of zygote

\*not performed in Canada

## Male Factors

- see [Urology, U37](#)

## Etiology

- varicocele (>40%)
- idiopathic (>20%)
- obstruction (~15%)
- cryptorchidism (~8%)
- immunologic (~3%)
- exogenous androgens

## Investigations

- semen analysis and culture



### Normal Semen Analysis (WHO lower reference limits)

- Must be obtained after 2-7 d of abstinence
- Volume 1.5 cc
- Count 15 million/cc
- Vitality 58% live
- Motility 32% progressive, 40% total (progressive + non-progressive)
- Morphology 4.0% normal



### Polycystic Ovarian Syndrome – HAIR-AN

Hirsutism, HyperAndrogenism, Infertility, Insulin Resistance, Acanthosis Nigricans

# Polycystic Ovarian Syndrome

## Etiology

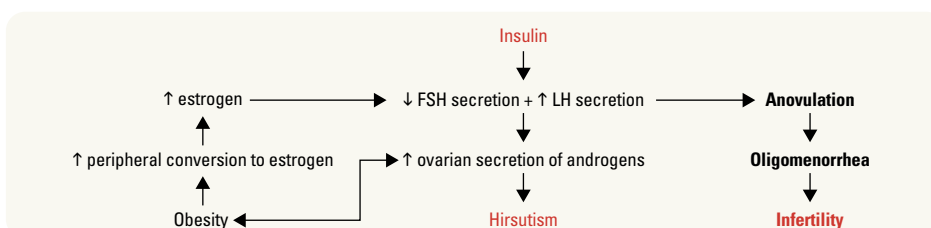


Figure 12. Pathophysiology of polycystic ovarian syndrome

## Diagnosis

- Rotterdam diagnostic criteria: 2 of 3 required
  - oligomenorrhea/irregular menses for 6 mo
  - hyperandrogenism
    - clinical evidence – hirsutism or acne
    - biochemical evidence – raised free testosterone
  - polycystic ovaries on U/S (not appropriate in adolescents)

## Clinical Features

- average age 15-35 yr at presentation
- in adolescents, wait at least 1-2 yr to make diagnosis as adolescence resembles PCOS
- abnormal/irregular uterine bleeding, hirsutism, infertility, obesity, virilization
- acanthosis nigricans: darkening of skin folds in intertriginous zones (indicative of insulin resistance)
- insulin resistance occurs in both lean and obese patients
- FMHx of DM

## Investigations

- assess BMI, BP, and fasting lipid profile at presentation
  - goal: identify hyperandrogenism or chronic anovulation and rule out specific pituitary or adrenal disease as the cause
- laboratory
  - prolactin, TSH, free T4
  - 17-hydroxyprogesterone, LH:FSH >2:1 (LH is chronically high with FSH mid-range or low (low sensitivity and specificity))
  - increased DHEAS, androstenedione, and free testosterone (most sensitive)
- transvaginal or transabdominal U/S: polycystic-appearing ovaries
  - “string of pearls” – 12 small follicles 2-9 mm, or increased ovarian volume (>10 cc)
- tests for insulin resistance or glucose tolerance
  - 75 g OGTT yearly (particularly if obese)
- consider endometrial biopsy if long-standing abnormal uterine bleeding to rule out hyperplasia
- rule out other causes of abnormal bleeding

## Treatment

- cycle control
  - lifestyle modification (decrease BMI, increase exercise) to decrease peripheral estrone formation
  - hormonal IUS, combined hormonal contraception or cyclic Provera® to prevent endometrial hyperplasia due to unopposed estrogen
  - oral hypoglycemic (e.g. metformin) if T2DM or if trying to become pregnant
  - tranexamic acid (Cyklokapron®) for menorrhagia only
- infertility
  - medical induction of ovulation: letrozole, clomiphene citrate, human menopausal gonadotropins (HMG (Pergonal®)), LHRH, recombinant FSH, and metformin
    - metformin may be used in conjunction with clomiphene citrate for ovulation induction
  - ovarian drilling (perforate the stroma), wedge resection of the ovary - rarely done
  - bromocriptine (if hyperprolactinemia)
- hirsutism
  - any OCP can be used
    - Diane 35® (cyproterone acetate): antiandrogenic
    - Yasmin® (drospirenone and ethinyl estradiol): spironolactone analogue (inhibits steroid receptors)
  - mechanical removal of hair
  - finasteride (5-α reductase inhibitor)
  - flutamide (androgen reuptake inhibitor)
  - spironolactone (androgen receptor inhibitor)



### PCOS may be confused with

- Late onset CAH (21-hydroxylase deficiency)
- Cushing's syndrome
- Ovarian and adrenal neoplasms
- Hyperprolactinemia
- Hypothyroidism



### Clinical Signs of Endocrine Imbalance

- Menstrual disorder/amenorrhea (80%)
- Infertility (74%)
- Hirsutism (69%)
- Obesity (49%)
- Impaired glucose tolerance (35%)
- DM (10%)



### Long-Term Health Consequences

- Hyperlipidemia
- Adult-onset DM
- Endometrial hyperplasia
- Subfertility
- Obesity
- Sleep apnea



### Diagnostic Criteria for Polycystic Ovary Syndrome: Pitfalls and Controversies

JOGC 2008;8:671-679

At present, there is no clear-cut definition of biochemical hyperandrogenemia, particularly since there is dependence on poor laboratory standards for measuring androgens in women. Clinical signs of hyperandrogenism are ill-defined in women with PCOS, and diagnosis of both hirsutism and polycystic ovarian morphology remains subjective. There is also the inappropriate tendency to assign ovulatory status solely on the basis of menstrual cycle history or poorly timed endocrine measurements. Therefore it is important as clinicians to recognize the multifactorial and complex nature of PCOS and place this in the context of our present diagnostic limitations.

# Gynaecological Infections

## Physiologic Discharge

- clear, white, flocculent, odourless discharge; pH 3.8-4.2
- smear contains epithelial cells, Lactobacilli
- increases with increased estrogen states: pregnancy, OCP, mid-cycle, PCOS, or premenarchal
- if increased in perimenopausal/postmenopausal woman, consider investigation for other effects of excess estrogen (e.g. endometrial cancer)

## Non-Physiologic Discharge

- etiology
  - genital tract infection
  - vulvovaginitis: candidiasis, trichomoniasis, BV, polymicrobial superficial infection
  - chlamydia, gonorrhea
  - pyosalpinx, salpingitis
  - genital tract inflammation (non-infectious)
  - local: chemical irritants, douches, sprays, foreign body, trauma, atrophic vaginitis, desquamative inflammatory vaginitis, focal vulvitis
  - neoplasia: vulvar, vaginal, cervical, endometrial
  - systemic: toxic shock syndrome, Crohn's disease, collagen vascular disease, dermatologic (e.g. lichen sclerosis)
  - IUD, OCP (secondary to progesterone)

## Vulvovaginitis

### PREPUBERTAL VULVOVAGINITIS

- clinical features: irritation, pruritus, discharge, vulvar erythema, vaginal bleeding (can be due to Group A *Streptococcus* and *Shigella*)
- etiology
  - non-specific vulvovaginitis is responsible for 25-75% of vulvovaginitis in prepubertal girls
  - there are a number of potential factors in children that increase the risk of vulvovaginitis:
    - ◆ lack of labial development
    - ◆ unestrogenized, thin mucosa
    - ◆ more alkaline pH (pH 7) than postmenarchal girls/women
    - ◆ obesity
    - ◆ poor hygiene (proximity of anus to vagina)
    - ◆ foreign bodies (most commonly toilet paper)
    - ◆ irritation by bubble baths, shampoos, perfumed soaps, and chemicals
  - localized skin disorders: lichen sclerosis, condyloma acuminata
  - trauma: accidental straddle injury, sexual abuse
  - infectious
    - ◆ pinworms
    - ◆ *Candida* (if using diapers or chronic antibiotics)
    - ◆ Group A *Streptococcus*, *S. aureus*, and *Shigella*
    - ◆ discovery of STI should raise suspicion of sexual abuse
  - other
    - ◆ polyps, tumour (ovarian malignancy)
    - ◆ psychosomatic vaginal complaints (specific to vaginal discharge)
    - ◆ endocrine abnormalities (specific to vaginal bleeding)
    - ◆ blood dyscrasia (specific to vaginal bleeding)
    - ◆ other systemic diseases: measles, chickenpox, scarlet fever, Epstein-Barr Virus, *Mycoplasma pneumoniae*-induced rash and mucositis, Stevens-Johnson syndrome, Crohn's disease, and Kawasaki disease have all been associated with vulvovaginal signs and symptom
- investigations
  - vaginal swab for culture (specifically state that it is a pre-pubertal specimen)
  - pH, wet-mount, and KOH smear in prepubertal adults only
- treatment
  - enhanced hygiene and local measures (handwashing, white cotton underwear, no nylon tights, no tight-fitting clothes, no sleeper pajamas, sitz baths, avoid bubble baths, use mild detergent, eliminate fabric softener, avoid prolonged exposure to wet bathing suits, urination with legs spread apart)
  - barrier cream (zinc oxide, also known as diaper cream) to protect vulvar skin
  - infectious: treat with antibiotics for organism identified



**Vulvovaginitis**  
Vulvar and vaginal inflammation



**Vulvar Hygiene**  
Recommend wipe front to back, wash vulva only with water, avoid daily pantyliners, avoid douching, no need for "feminine cleansers/sprays/powders", use gentle laundry detergents for underwear, cotton underwear, no underwear at night



**Prepubertal and Adolescent Gynaecological Infections: Legal Aspects of Confidentiality**

- Clinicians who treat adolescents must be aware of federal, state, and provincial laws related to adolescent consent and confidentiality
- Clinicians must be aware of guidelines governing funding sources for particular services and be familiar with the consent and confidentiality policies of the facility in which they practice



Most common gynaecological problem in prepubertal girls is non-specific vulvovaginitis, not yeast

**Table 14. Other Common Causes of Vulvovaginitis in Prepubertal Girls**

	Pinworms	Lichen Sclerosis	Foreign Body
<b>Diagnosis</b>	Cellophane tape test	Area of white patches and thinning of skin (figure of 8)	Careful examination with or without sedation
<b>Treatment</b>	Empirical treatment with mebendazole	Topical steroid creams	Irrigation of vagina with saline, may require local anesthesia or an exam under anesthesia

**INFECTIOUS VULVOVAGINITIS****Table 15. Infectious Vulvovaginitis**

	Candidiasis	Bacterial Vaginosis (BV)	Trichomoniasis
<b>Organisms</b>	<i>Candida albicans</i> (90%) <i>Candida glabrata</i> (<5%) <i>Candida tropicalis</i> (<5%)	Replacement of vaginal Lactobacillus with: <i>Gardnerella vaginalis</i> <i>Mycoplasma hominis</i> Anaerobes: <i>Prevotella</i> , <i>Mobiluncus</i> , <i>Bacteroides</i>	<i>Trichomonas vaginalis</i> (flagellated protozoan)
<b>Risk Factors</b>	Immunosuppression (DM, AIDS, etc.) Recent antibiotic use Increased estrogen levels (e.g. pregnancy, OCP)	High frequency of vaginal intercourse Smoking Douching	Sexual transmission
<b>Discharge</b>	Whitish, "cottage cheese," minimal	Grey, thin, diffuse, fishy smelling	Yellow-green, malodorous, diffuse, frothy
<b>% asymptomatic</b>	20% asymptomatic	50-75% asymptomatic	25% asymptomatic
<b>Signs/Symptoms</b>	Intense pruritus Swollen, inflamed genitals Vulvar burning, dysuria, dyspareunia	Fishy odour, especially after coitus Absence of vulvar/vaginal irritation	Petechiae on vagina and cervix Occasionally irritated, tender vulva Dysuria, frequency
<b>pH</b>	≤4.5	≤4.5	≤4.5
<b>Saline Wet Mount</b>	KOH wet mount reveals hyphae and spores	>20% clue cells = squamous epithelial cells dotted with coccobacilli ( <i>Gardnerella</i> ) Paucity of WBC Paucity of <i>Lactobacilli</i> Positive whiff test: fishy odour with addition of KOH to slide (due to formation of amines)	Motile flagellated organisms Many WBC Inflammatory cells (PMNs) Can have positive whiff test
<b>Treatment</b>	Clotrimazole, butoconazole, miconazole, terconazole suppositories, and/or creams for 1, 3, or 7 d treatments Only vaginal treatment in pregnancy Fluconazole 150 mg PO in single dose	No treatment if non-pregnant and asymptomatic, unless scheduled for pelvic surgery or procedure <b>Oral</b> Metronidazole 500 mg PO BID x 7 d* Oral treatment is best in pregnancy <b>Vaginal</b> Metronidazole 0.75% gel x 5 d once daily Clindamycin 2% 5 g intravaginally at bedtime for 7 d Probiotics ( <i>Lactobacillus</i> sp.): oral or topical alone or as adjuvant	Treat even if asymptomatic Metronidazole 2 g PO single dose or metronidazole 500 mg BID x 7 d (alternative) Symptomatic pregnant women should be treated with metronidazole 2 g once
<b>Other</b>	Prophylaxis for recurrent infection includes boric acid, vaginal suppositories, luteal phase fluconazole Routine treatment of partner(s) not recommended (not sexually transmitted)	Associated with recurrent preterm labour, preterm birth, and postpartum endometritis Routine treatment of partner(s) not recommended (not sexually transmitted)	Treat partner(s) (sexually transmitted)

\* Need to warn patients on metronidazole not to consume alcohol (disulfiram-like action)

## Sexually Transmitted Infections

- see [Family Medicine, FM46](#)

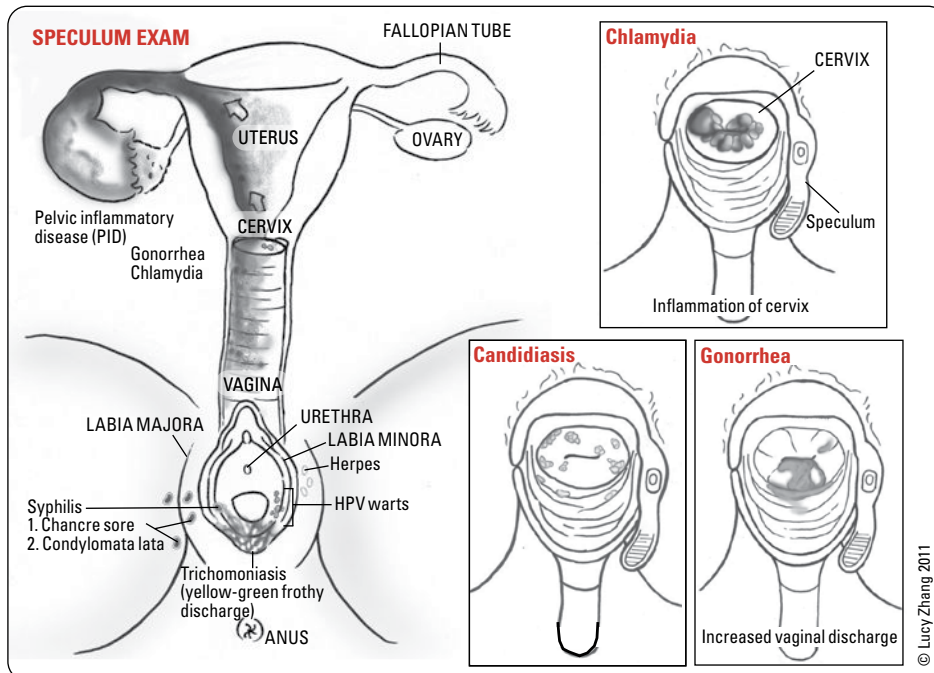


Figure 13. Speculum exam

### TRICHOMONIASIS

- see [Infectious Vulvovaginitis, GY27](#)

### CHLAMYDIA

#### Etiology

- *Chlamydia trachomatis*

#### Epidemiology

- most common bacterial STI in Canada
- often associated with *N. gonorrhoeae*

#### Clinical Features

- asymptomatic (80% of women)
- muco-purulent endocervical discharge
- urethral syndrome: dysuria, frequency, pyuria, no bacteria on culture
- pelvic pain
- postcoital bleeding or intermenstrual bleeding (particularly if on OCP and prior history of good cycle control)
- symptomatic sexual partner

#### Investigations

- cervical culture or nucleic acid amplification test (can present in pharynx, rectum)
- obligate intracellular parasite: tissue culture is the definitive standard
- urine and self vaginal tests now available, which are equally or more effective than cervical culture

#### Treatment

- doxycycline 100 mg PO BID for 7 d or azithromycin 1 g PO in a single dose. Doxycycline is contraindicated in the 2nd and 3rd trimesters of pregnancy
- reportable disease, test and provide empiric treatment to all sexual partners of the index case within 60 d prior to symptom onset or date of specimen collection (if the index case is asymptomatic)
- test of cure is recommended 3 wk after completion of treatment when compliance to treatment is suboptimal, an alternative treatment regimen is used, or the person is prepubertal or pregnant

#### Screening

- during pregnancy
- asymptomatic sexually active people under 25 yr
- neonates born to mothers with chlamydia
- any other people with risk factors for sexually transmitted and blood-borne infection



#### CDC Notifiable Diseases

- Chancroid
- Chlamydia
- Gonorrhea
- Hepatitis A, B, C
- HIV
- Syphilis



#### Risk Factors for STIs

- History of previous STI
- Contact with infected person
- Sexually active individual <25 yr
- Multiple partners
- New partner in last 3 mo
- Lack of barrier protection use
- Social factors (homelessness, drug use)



#### STI Testing

- Vaginal swab
- Tests for bacterial vaginosis, trichomoniasis, *Candida*
- Cervical swab
- Tests for gonorrhea and chlamydia



Test of cure for *C. trachomatis* and *N. gonorrhoeae* is not routinely indicated. Repeat testing if symptomatic, if compliance with treatment is uncertain, or if pregnant.

## Complications

- PID: low-grade salpingitis and adhesions resulting in tubal obstruction
- infertility
- ectopic pregnancy
- chronic pelvic pain
- Fitz-Hugh-Curtis syndrome (liver capsule inflammation)
- reactive arthritis (male predominance, HLA-B27 associated), conjunctivitis, urethritis
- perinatal infection: conjunctivitis, pneumonia

## GONORRHEA

### Etiology

- *Neisseria gonorrhoeae*
- symptoms and risk factors same as chlamydia

### Investigations

- Gram stain shows Gram-negative intracellular diplococci
- cervical, rectal, and throat culture (if clinically indicated)

### Treatment

- single dose of ceftriaxone 250 mg IM plus azithromycin 1 g PO
  - if pregnant: above regimen or spectinomycin 2 g IM plus azithromycin 1 g PO (avoid quinolones)
  - also treat chlamydia, due to high rate of co-infection
- treat partners
  - reportable disease
  - screening as with chlamydia

## HUMAN PAPILLOMAVIRUS

### Etiology

- most common viral STI in Canada
- >200 subtypes, of which >30 are genital subtypes
- HPV types 6 and 11 are classically associated with anogenital warts/condylomata acuminata
- HPV types 16 and 18 are the most oncogenic (classically associated with cervical HSIL)
- types 16, 18, 31, 33, 35, 36, 45 (and others) associated with increased incidence of cervical and vulvar intraepithelial hyperplasia and carcinoma
  - HPV is readily transmissible between opposite- and same-sex partners through receptive and penetrative vaginal, anal, and oral sex, and non-penetrative sex (digital-vaginal sex and skin-to-skin contact)
  - infection with one HPV type does not appear to provide protection against infection with related HPV types

### Clinical Features

- latent infection
  - no visible lesions, asymptomatic
  - only detected by DNA hybridization tests
- subclinical infection
  - visible lesion found during colposcopy or on Pap test
- clinical infection
  - visible wart-like lesion without magnification (check pharynx too)
  - hyperkeratotic, verrucous or flat, macular lesions
  - vulvar edema

### Investigations

- cervical cytology by Pap test
  - koilocytosis: nuclear enlargement and atypia with perinuclear halo
- biopsy of lesions at colposcopy
- detection of HPV DNA subtype using nucleic acid probes (not routinely done but can be done in presence of abnormal Pap test to guide treatment)

### Treatment

- anogenital warts
  - patient administered
    - ◆ podofilox 0.5% solution or gel BID x 3 d in a row (4 d off) then repeat x 4 wk
    - ◆ imiquimod (Aldara®) 5% cream 3x/wk nightly x 16 wk
    - ◆ sinecatechins 10% ointment 0.5 cm strand TID x up to 16 wk, daily dose ≤ 250 mg (need not be washed off)



### Genital Warts During Pregnancy

- Condyloma tend to get larger in pregnancy and should be treated early (consider excision)
- Removal only if obstructing birth canal or risk of extensive bleeding
- Do not use imiquimod, podophyllin, or podofilox in pregnancy
- Baby at risk for juvenile respiratory papillomatosis, but cone dissection does not significantly reduce the risk



### Human Rights in Health Equity: Cervical Cancer and HPV Vaccines

Am J Law Med 2009;35:365-387

- While cervical cancer rates have drastically fallen in developed countries due to effective prevention and treatment, socially disadvantaged women within these countries remain disproportionately more likely to develop and die of cervical cancer.
- In most developing countries cervical cancer rates have risen or remained unchanged.
- It must be recognized that cervical cancer disparities between race groups, urban and rural residence, and high and low socioeconomic status are attributed to disparate screening and vaccination coverage.
- Programs are implemented without sufficient attention to conditions that render screening less effective or inaccessible to disadvantaged social groups including: lack of information, undervaluing of preventive care, opportunistic delivery in limited healthcare settings, sexual health stigma, and related privacy concerns.



### A 9-Valent HPV Vaccine Against Infection and Intraepithelial Neoplasia in Women

NEJM 2015;372:711-723

**Purpose:** To determine the efficacy and immunogenicity of the qHPV (types 6, 11, 16, 18) vs. 9vHPV (five additional types 31, 33, 45, 52, 58) vaccines.

**Method:** International randomized, double-blinded phase 2B-3 study of 9vHPV vaccine in 14215 women between ages of 16-26. Participants were randomized to the 9vHPV vaccine group or the qHPV vaccine group and each received a series of three IM injections (d 1, 2 mo, and 6 mo). Swabs of labial, vulvar, perineal, perianal, endocervical, and ectocervical tissue was obtained and used for HPV DNA testing/Pap smear.

**Results:** Rate of high-grade cervical, vulvar, or vaginal disease was 14.0 per 1000 person-yr in both vaccine groups. The rate of high-grade cervical, vulvar, or vaginal disease related to HPV-31, 33, 45, 52, and 58 was 0.1 per 1000 person-yr in the 9vHPV group and 1.6 per 1000 person-yr in the qHPV group (95% CI=80.9-99.8). Antibody responses to HPV-6, 11, 16, and 18 were not significantly different between the two vaccine groups although adverse events related to injection sites were more common in the 9vHPV group.

**Conclusions:** The 9vHPV vaccine was non-inferior to qHPV vaccine in preventing infection and disease related to HPV-6, 11, 16, and 18 and also covered additional oncogenic types HPV-31, 33, 45, 52, and 58 in a susceptible population.



- provider administered
  - ◆ cryotherapy with liquid nitrogen: repeat q1-2 wk
  - ◆ podophyllin resin in tincture of benzoin: weekly
  - ◆ trichloroacetic acid (TCA) (80-90%) or bichloroacetic acid weekly x 4-6 wk; safe in pregnancy
  - ◆ surgical removal/laser
- intraepithelial lesions and cancers (See [Gynaecological Oncology, GY42](#))

### Prevention

- vaccination: Gardasil®9, Gardasil®, Cervarix® (see [Table 28, GY49](#))
- condoms may not fully protect (areas not covered, must be used every time throughout entire sexual act)

## HERPES SIMPLEX VIRUS OF VULVA

### Etiology

- 90% are HSV-2, 10% are HSV-1

### Clinical Features

- may be asymptomatic
- initial symptoms: average incubation is 4 d after exposure (range 2-12 d)
- prodromal symptoms: tingling, burning, and pruritus
- multiple, painful, shallow ulcerations with small vesicles appear 7-10 d after initial infection (absent in many infected persons); lesions are infectious
- inguinal lymphadenopathy, malaise, and fever often with first infection
- dysuria and urinary retention if urethral mucosa affected
- recurrent infections: common but less severe, less frequent, and shorter in duration (usually only HSV-2)

### Investigations

- viral culture preferred in patients with ulcer present; however, decreased sensitivity as lesions heal
- HSV DNA PCR
- cytologic smear (Tzanck smear) shows multinucleated giant cells, limited use due to low sensitivity and specificity
- type specific serologic tests for antibodies to HSV-1 and HSV-2 (not routinely available in Canada)

### Treatment

- first episode: acyclovir 200 mg PO five times daily x 7-10 d, famciclovir 250 mg PO TID x 7-10 d, or valacyclovir 1 g PO BID x 7-10 d
- recurrent episode: acyclovir 400 mg PO TID x 5 d, famciclovir 125 mg PO BID x 5 d, or valacyclovir 1 g PO once daily x 5 d
- daily suppressive therapy
  - consider for >6 recurrences per yr or recurrence every 2 mo
  - acyclovir 400 mg PO BID, famciclovir 250 mg PO BID, valacyclovir 500 mg PO once daily, or valacyclovir 1 g PO once daily
- severe disease: IV acyclovir 5-10 mg/kg IV q8 h x 2-7 d or until clinical improvement observed followed by oral antiviral therapy to complete 10 d of total therapy
- education regarding transmission: avoid sexual contact from onset of prodrome until lesions have cleared, use barrier contraception

## SYPHILIS

### Etiology

- *Treponema pallidum*

### Classifications

- primary syphilis
  - 3-4 wk after exposure (median incubation 21 d)
  - painless chancre on vulva, vagina, or cervix
  - painless inguinal lymphadenopathy
  - serological tests usually negative, local infection only
- secondary syphilis (can resolve spontaneously)
  - 2-6 mo after initial infection, in 25% of patients with untreated primary syphilis
  - nonspecific symptoms: malaise, anorexia, headache, and diffuse lymphadenopathy
  - generalized maculopapular rash: palms, soles, trunk, and limbs
  - condylomata lata: anogenital, broad-based, fleshy, grey lesions
  - serological tests usually positive
- latent syphilis
  - no clinical manifestations; detected by serology only



### Epidemiology of Genital Ulcers

HSV	70-80%
1° Syphilis	5%
Chancroid ( <i>Haemophilus ducreyi</i> )	<1%



- tertiary syphilis
  - may involve any organ system
  - neurological: tabes dorsalis, and general paresis
  - cardiovascular: aortic aneurysm and dilated aortic root
  - vulvar gumma: nodules that enlarge, ulcerate, and become necrotic (rare)
- congenital syphilis
  - may cause fetal anomalies, stillbirths, or neonatal death

### Investigations

- aspiration of ulcer serum or node
- darkfield microscopy (most sensitive and specific diagnostic test for syphilis): look for spirochetes
- non-treponemal screening tests (VDRL, RPR); non-reactive after treatment, can be positive with other conditions
- specific anti-treponemal antibody tests (FTA-ABS, MHA-TP, TP-PA)
  - confirmatory tests; remain reactive for life (even after adequate treatment)

### Treatment

- reportable disease, partners should be referred for treatment
- treatment of primary, secondary, latent syphilis of <1 yr duration
  - benzathine penicillin G 2.4 million units IM single dose
- treatment of latent syphilis of >1 yr duration
  - benzathine penicillin G 2.4 million units IM q1 wk x 3 wk
- treatment of neurosyphilis
  - IV aqueous penicillin G 3-4 million units q4 h x 10-14 d
- screening
  - high-risk groups (partner with syphilis, HIV-infected individuals, high risk sexual behaviour, history of incarceration)
  - in pregnancy (see [Obstetrics](#), [Infections During Pregnancy](#), OB31)

### Complications

- if untreated, 25-40% will experience late complications

### HIV

- see [Infectious Diseases](#), ID26

## Bartholin Gland Abscess

### Etiology

- follows the infection of an obstructed Bartholin duct
- most commonly *E. coli*, polymicrobial, *S. aureus*, and Group B *Strep*

### Clinical Features

- unilateral swelling and pain in inferior lateral opening of vagina
- sitting and walking may become difficult and/or painful

### Treatment

- large mass >3 cm
  - 1st or 2nd episode: I&D under local anesthesia with placement of Word catheter (10 French latex catheter) for 2-3 wk
  - recurrence after two failed attempts with Word catheter: marsupialization in OR
- small mass <3 cm
  - I&D with Word catheter, sitz baths, warm compresses
- antibiotics: reserved for patients with recurrence, high risk of complicated infection, culture-positive MRSA, systemic infection

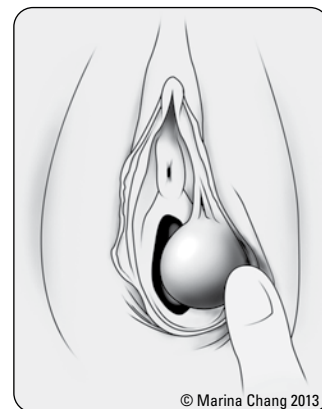


Figure 14. Bartholin gland abscess

## Pelvic Inflammatory Disease

- up to 20% of all gynaecology-related hospital admissions
- inflammation of the upper genital tract (above the cervix) including endometrium, fallopian tubes, ovaries, pelvic peritoneum ± contiguous structures that primarily affects young, sexually active women



PID accounts for up to 20% of all gynaecological hospital admissions

### Etiology

- microbial etiology unknown in most cases, often considered a polymicrobial infection
- causative organisms (in order of frequency)
  - *C. trachomatis*
  - *N. gonorrhoeae*
    - ♦ gonorrhea and chlamydia often co-exist
  - *M. genitalium*
  - *E. coli* and colonic anaerobes found in rare cases of PID in post-menopausal women
  - very rare pathogens: *M. tuberculosis*, *H. influenzae*, *S. pneumoniae*, and the agents of actinomycosis

### Risk Factors

- age 15-25 yr
- multiple partners, STI in partner
- previous PID
- IUD (extremely rare, occurs within first 3 wk after insertion)

### Clinical Features

- wide spectrum of clinical presentation: time course typically acute although many women will have subclinical PID that does not prompt a patient to present for medical care but severe enough to cause significant sequelae (fertility issues)
- clinical diagnosis of PID: fever  $>38.3^{\circ}\text{C}$ , lower abdominal pain and tenderness, and abnormal discharge (cervical or vaginal)
- uncommon: N/V, dysuria, and AUB
- chronic disease (often due to chlamydia)
  - constant pelvic pain
  - dyspareunia
  - palpable mass
  - very difficult to treat, may require surgery

### Investigations

- blood work
  - $\beta$ -hCG (must rule out ectopic pregnancy), CBC, blood cultures if suspect septicemia
- urine routine and microscopy (R&M)
- speculum exam, bimanual exam
  - vaginal swab for Gram stain, C&S
  - nucleic acid amplification tests (NAAT) for *N. gonorrhoeae*, *C. trachomatis*, *M. genitalium*
  - HIV testing and serologic testing for syphilis
- ultrasound
  - may be normal
  - free fluid in cul-de-sac
  - pelvic or tubo-ovarian abscess
  - hydrosalpinx (dilated fallopian tube)
- laparoscopy and endometrial biopsy (uncommonly performed)
  - only done in patients that have failed outpatient treatment, symptoms not improving after 72 h of inpatient treatment, or unclear diagnosis
  - surgery has high specificity but low sensitivity

### Treatment

- must treat with polymicrobial coverage
- percutaneous drainage of abscess under U/S guidance
- laparoscopic drainage when no response to treatment, surgical (salpingectomy, TAH/BSO) if failure
- consider removing IUD after a minimum of 24 h of treatment
- reportable disease, treat partners
- consider re-testing for *C. trachomatis* and *N. gonorrhoeae* 4-6 wk after treatment if documented infection



#### PID Diagnosis

##### Minimum diagnostic criteria

- Cervical motion tenderness
- Uterine tenderness
- Adnexal tenderness

##### Additional diagnostic criteria

- Oral temperature  $>38.3^{\circ}\text{C}$
- Leukocytosis on saline microscopy of vaginal secretions/wet mount
- Elevated ESR or CRP
- Laboratory documentation of cervical infection with *N. gonorrhoeae* or *C. trachomatis*

##### Definitive diagnostic criteria

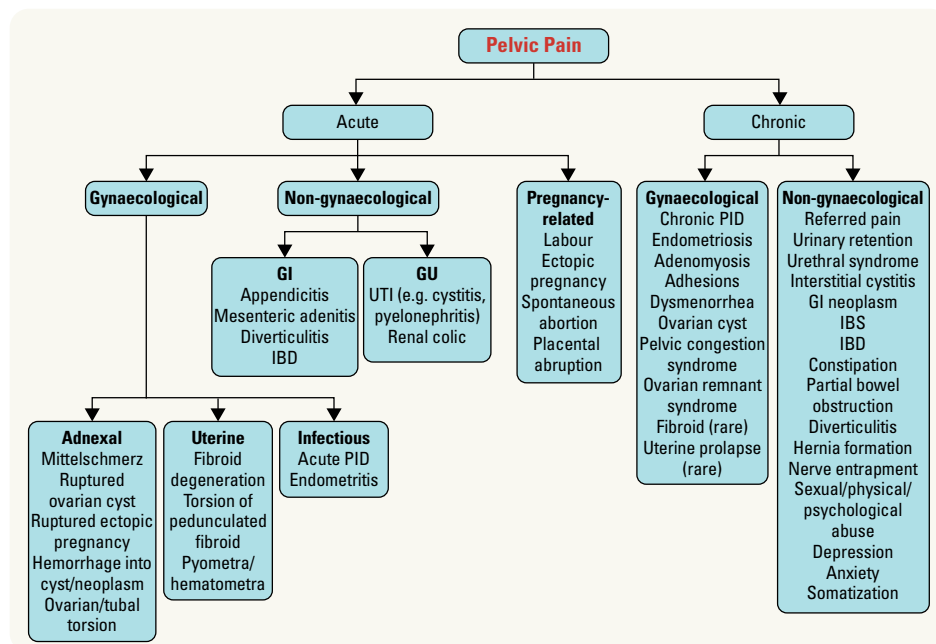
- Endometrial biopsy with histopathologic evidence of endometritis
- Transvaginal sonography or MRI showing thickened fluid-filled tubes, free fluid or tubo-ovarian complex
- Gold standard: laparoscopy demonstrating abnormalities consistent with PID

**Table 16. Inpatient and Outpatient Management Options for Pelvic Inflammatory Disease**

	Inpatient	Outpatient
<b>Indications</b>	Moderate to severe illness Atypical infection Adnexal mass, tubo-ovarian mass, or pelvic abscess Failed or cannot tolerate oral therapy Immunocompromised Pregnant Adolescent (first episode) Surgical emergency cannot be excluded (e.g. ovarian torsion) PID is secondary to instrumentation	Typical findings Mild to moderate illness Oral antibiotics tolerated Compliance ensured Follow up within 48-72 h (to ensure symptoms not worsening)
<b>Antibiotic Regimen</b>	Cefoxitin 2 g IV q6 h + doxycycline 100 mg PO/IV q12 h or Clindamycin 900 mg IV q8h + gentamycin 2 mg/kg IV/IM loading dose then gentamycin 1.5 mg/kg q8h maintenance dose Continue IV antibiotics for 24 h after symptoms have improved then doxycycline 100 mg PO BID to complete 14 d (add metronidazole 500 mg PO BID x 14 d in patients with tubo-ovarian abscess)	1st line: ceftriaxone 500 mg IM x 1 dose + doxycycline 100 mg PO BID x 14 d or cefoxitin 2 g IM x 1 dose + probenecid 1 g PO + doxycycline 100 mg PO BID ± metronidazole 500 mg PO BID x 14 d 2nd line: ofloxacin 400 mg PO BID x 14 d or levofloxacin 500 mg PO once daily x 14 d ± metronidazole 500 mg PO BID x 14 d

**Complications of Untreated Pelvic Inflammatory Disease**

- chronic pelvic pain
- persistent hydrosalpinx
- abscess, peritonitis
- adhesion formation
- ectopic pregnancy
- infertility
  - 1 episode of PID: 13% infertility
  - 2 episodes of PID: 36% infertility
- bacteremia
- septic arthritis, endocarditis

**Figure 15. Approach to pelvic pain****Toxic Shock Syndrome (TSS)**

- see [Infectious Diseases, ID22](#)
- Staphylococcal toxic shock syndrome (TSS) is a clinical illness characterized by rapid onset of fever, rash, hypotension, and multiorgan system involvement

**Risk Factors**

- menstrual TSS
  - significantly decreased as a result of the withdrawal of highly-absorbent tampons and polyacrylate rayon-containing products from the market; however, tampon use remains a risk factor for TSS (high absorbency, tampons used continuously for more days of their cycle, and keeping a single tampon in place for a longer period of time)

**Toxic Shock Syndrome**

Multiple organ system failure due to *S. aureus* exotoxin (rare condition)

- non-menstrual TSS (gynaecologic)
  - diaphragm, cervical cap, or sponge use (prolonged use, i.e. >24 h)
  - surgical and postpartum wound infections, mastitis, sinusitis, osteomyelitis, arthritis, burns, cutaneous lesions, etc.

### Clinical Features

- sudden high fever/chills
- sore throat, headache, and diarrhea
- macular erythroderma followed by desquamation 1-2 wk later
- signs of multisystem organ failure
- refractory hypotension

### Treatment

- treatment of shock
- remove potential sources of infection (foreign objects)
- surgical debridement (if warranted)
- adequate hydration
- empiric antibiotic therapy with vancomycin (load 20-35 mg/kg and maintenance 15-20 mg/kg q8-12 h) + clindamycin 900 mg IV q8 h + piperacillin-tazobactam 4.5 g IV q6 h
- continue combination therapy until patient is hemodynamically stable for at least 48-72 h

## Surgical Infections

### Postoperative Infections in Gynaecological Surgery

- pelvic cellulitis
  - common post hysterectomy, affects vaginal vault
  - erythema, induration, tenderness, and discharge involving vaginal cuff
  - if fever and leukocytosis, treat with broad-spectrum ABx (i.e. clindamycin and gentamicin)
  - drain if excessive purulence or large mass
  - can result in intra-abdominal and pelvic abscess
- see [General and Thoracic Surgery, Postoperative Fever, GS8](#)

## Sexual Abuse

- see [Emergency Medicine, ER27](#) and [Family Medicine, FM30](#)

## Sexuality and Sexual Dysfunction

### SEXUAL RESPONSE

1. desire: energy that allows an individual to initiate or respond to sexual stimulation (libido)
2. arousal: physical and emotional stimulation leading to breast and genital vasodilation and clitoral engorgement (excitement)
3. orgasm: physical and emotional stimulation is maximized, allowing the individual to relinquish their sense of control
4. resolution: most of the congestion and tension resolves within seconds, complete resolution may take up to 60 min

**Note:** this framework cannot be applied consistently to women's sexual response. For many women, the phases may vary in sequence, overlap, repeat, or be absent during some or all sexual encounters

### SEXUAL DYSFUNCTION

#### Classification

- lack of desire (most common)
- lack of arousal
- anorgasmia
  - primary anorgasmia: never before achieved orgasm under any circumstances
  - secondary anorgasmia: was able to achieve orgasms before but unable to achieve orgasms presently
- dyspareunia: painful intercourse, superficial, or deep

#### Etiology

- biological:
  - gynaecological (e.g. pregnancy, childbirth, menopausal atrophy, endometriosis, prolapse, urinary incontinence)
  - urological (e.g. recurrent bacterial cystitis, chronic renal failure)
  - vascular (e.g. peripheral vascular disease, CAD)
  - neurological dysfunction (e.g. nerve entrapment syndrome, spinal cord injury, multiple sclerosis, Parkinson's)

- musculoskeletal (e.g. arthritis, mechanical back pain)
- systemic health disorders (e.g. DM, thyroid disorders)
- medication side effects (e.g.  $\beta$ -blockers, benzodiazepines, SSRIs, antipsychotics, oral contraceptives)
- behavioural or lifestyle (e.g. smoking, alcohol consumption, opioids, obesity)
- psychological:
  - early events: history of sexual violence, unpleasant early sexual experiences, or growing up in a family or society that communicates no information or negative messages about women's sexuality
  - current events: depression, anxiety, psychosis, fatigue, stress, or other mental health disorders
- relationship:
  - abuse
  - relationship distress
  - failure to engage in effective sexual stimulation

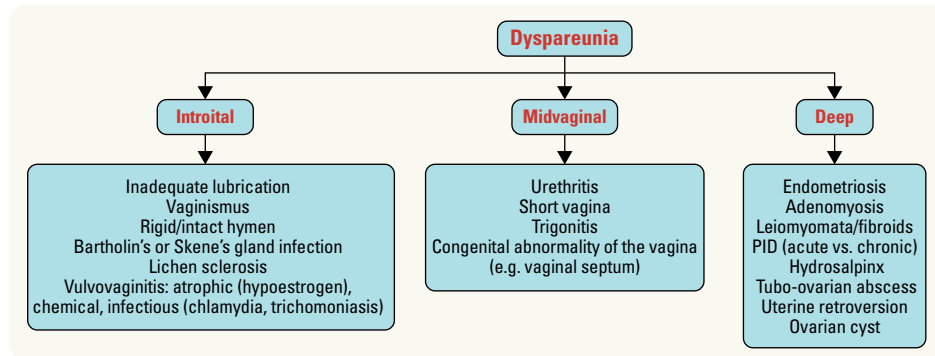


Figure 16. Approach to dyspareunia

### Treatment

- general:
  - assess patient goals and construct a safety plan as needed
  - counseling
  - lifestyle changes
  - improve body image
- lack of desire:
  - biological: rule out other conditions/medication side effects; consider sildenafil for SSRI side effects; consider androgens (testosterone, DHEA), estrogens, tibolone; consider serotonergic and dopaminergic agents: flibanserin, bupropion, buspirone; consider bremelanotide
  - psychological: rule out/treat depression, other mental health issues
  - relationship: assess couple interaction and partner sexual function; treat partner and relationship conflict
- concerns with arousal/lubrication:
  - biological: non-hormonal, water-based lubricants; consider estrogen (topical cream, tablet, or ring)
  - psychological: address sexual anxieties
  - relationship: education regarding slowing of sexual response with aging
- anorgasmia:
  - biological: augment stimulation  $\pm$  vibrator; consider androgens
  - psychological: sex education, anxiety reduction, and use of erotica
  - relationship: stimulation needs and helping patient teach partner what they need
- sexual pain disorders:
  - biological: rule out other conditions; topical estrogen if atrophy; consider nerve modulators (amitriptyline, gabapentin, or pregabalin)
  - psychological: sex therapy if vaginismus
  - relationship: rule out abuse (with patient alone)

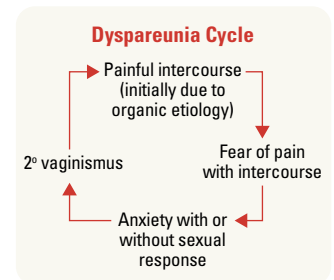


Figure 17. Dyspareunia cycle



#### Kegel Exercises

Regular contraction and relaxation to strengthen pelvic floor muscles

#### Reverse Kegel Exercises

1 s contraction then 5 s of relaxation